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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,043	06/15/2005	Philippe Soucaille	GC743-2-US	6139

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1637	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,043	SOUCAILLE ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *1-21 and 28-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/10/2006; 9/01/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group II, claims 20-27 in the reply filed on May 9, 2007 is acknowledged. It is also noted that under the Ochiai guidelines, if the product is found allowable, and the method claims remain commensurate in scope, rejoinder of the method claims is permitted.

Claim InterpretationSeveral of the terms in the claims lack specific structural requirements. Speciifcally, the term "fragment homologous" in claim 22, step a) imposes no specific structural requirement on the final library, since any sequence has some level of homology to other sequences, sharing at least a single nucleotide in common. Separately, the requirements in claims 23, 24, 26 and 27 which require a "substitution" lack a reference sequence against which the term "substitution" is matched. Any sequence is "substituted" relative to some other, different sequence. In the absence of a limiting structure, this element imposes no structural requirements on the claim.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 22-24, 26 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Hartley et al (U.S. Patent 5,888,732) as evidenced by Sizemore et al (Nucleic Acids Research (1990) 18(10):2875-2880).

Hartley teaches a mixture of double stranded polynucleotides, which include in sequential order:

a) a nucleic acid fragment homologous to an upstream region of a chromosomal gene of interest (see figure 4F, where there is an SP6 promoter element),

b) a first recombinase site (see figure 4F, where immediately adjacent to the SP6 promoter element is a LoxP recombinase site),

c) a nucleic acid encoding an antimicrobial resistance gene (see figure 4F, where the Tetracycline and ampicillin resistance genes continue counter clockwise from the SP6 promoter element and the LoxP recombinase site),

d) a second recombinase site (see figure 4F, where a second loxP site is present after the Tet and Amp genes),

e) two consensus regions of a promoter and a linker sequence, wherein the first consensus region comprises a -35 region, the second consensus region comprises a -10 region and the linker sequence comprises at least 14 - 20 nucleotides and is flanked by the first consensus region and wherein the -35 region and the -10 region each include between 4 - 6 conserved nucleotides of corresponding consensus regions of the promoter (see figure 4F where Hartley teaches the tetOP promoter and see column 6, where Hartley refers to Sizemore

for the promoter. Sizemore evidences, as shown in figure 1 below, a promoter with a –35 region, a –10 region, with 14 nucleotides between the regions)

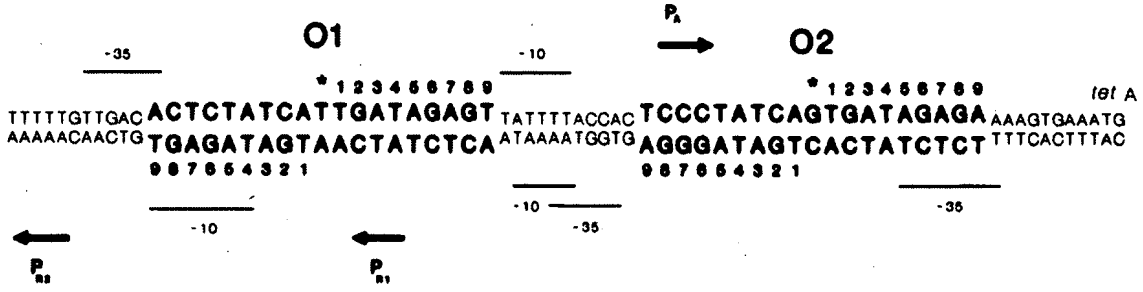

Fig.1 Nucleotide sequence of the Tn*10* encoded wild type *tet* regulatory region. The sequence of the tandem *tet* operators O_1 and O_2 is displayed in bold and enlarged print, the palindromic center is marked with a star. The numbering above and underneath the sequence designates the positions within each operator. The tandem, overlapping promoters P_{R1} and P_{R2}, responsible for transcription of the *tetR* gene are shown in the lower half of the figure, the promoter P_A, responsible for transcription of the *tetA* gene is shown in the upper half of the figure. The bold arrows define the direction, their blunt ends correspond to the respective starting points of transcription.

f) a nucleic acid fragment homologous to the downstream region of the +1 transcription start site of the promoter (see figure 4F, where the LacUV5 or CMV promoters will have seuqences that are at least partially homologous to a downstream regions of the +1 transcription start site (they will share at least one nucleotide in common).

With regard to claim 23, Sizemore includes a ribosome binding site between the –10 region and the +1 region, therefore the vector in figure 4F of Hartley inherently includes such a site.

With regard to claim 24, Sizemore includes a start codon between the –10 region and the +1 region, therefore the vector in figure 4F of Hartley inherently includes such a site.

With regard to claim 26, Sizemore teaches a particular –35 regions, which is substituted relative to other –35 sequences in existence, therefore the vector in figure 4F of Hartley inherently includes such a site.

With regard to claim 27, Sizemore teaches a particular –10 regions, which is substituted relative to other –10 sequences in existence, therefore the vector in figure 4F of Hartley inherently includes such a site.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 22-24, 26 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jensen et al (WO 98/07846) in view of Israelsen et al (App. Environ. Microbiol. (1995) 61(7):2540-2547) and further in view of Elledge et al (U.S. Patent 6,828,093).

Jensen teaches an artificial promoter library comprising mixture of double stranded polynucleotides, which include in sequential order:

a) a nucleic acid fragment homologous to an upstream region of a chromosomal gene of interest (see page 19, lines 5-25, where the pAK80 vector has a PCT 1138 replicon sequence that is "upstream" of some gene),

b) a first cloning site (see page 19, lines 25-30, where the pAK80 vector is used, and the map is shown below, which has an EcoRI site clockwise of the PCT 1138 sequence),

c) a nucleic acid encoding an antimicrobial resistance gene (see page 20, line 5 and see Israelsen, figure 2, shown below, which has the erm or erythromycin gene sequence clockwise of the EcoRI site),

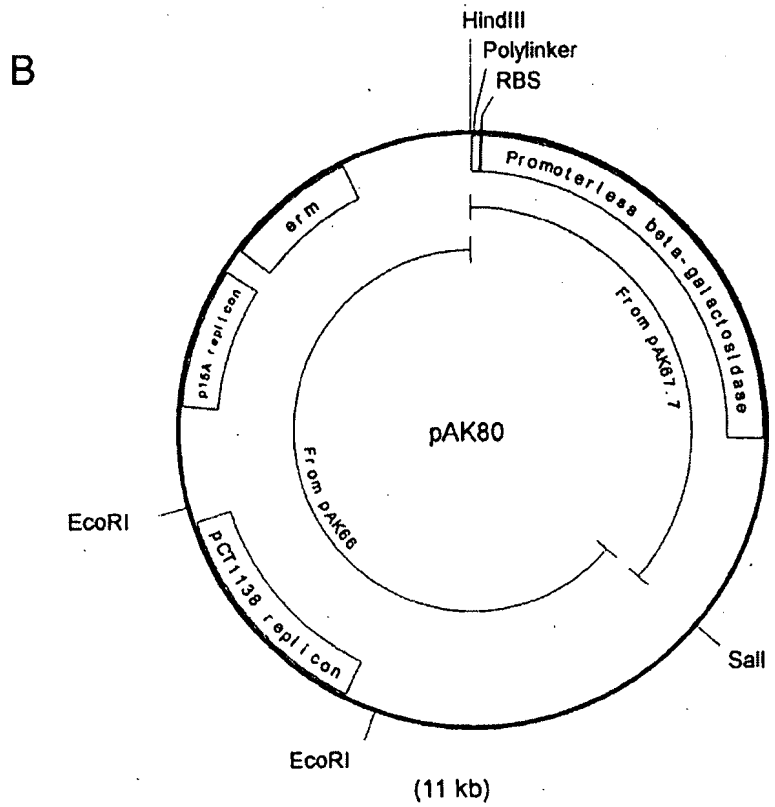

FIG. 2. (A) Polylinker and sequences upstream of the β-galactosidase gene in pAK67.7 and pAK80. Restriction sites which are unique in pAK80 are indicated. R.B.S. indicates the putative ribosome binding site. The last 3 bp constitute the first codon in *lacL*. Stop codons are designated with an asterisk. (B) Physical map of the promoter probe vector pAK80. DNA fragments from pAK66 and pAK67.7 and the restriction sites for construction of pAK80 are indicated. The polylinker region is illustrated in Fig. 2A. RBS indicates the putative ribosome binding site. *erm* is the erythromycin resistance gene.

d) a second cloning site (see HindIII site, clockwise of the erm site),

e) two consensus regions of a promoter and a linker sequence, wherein the first consensus region comprises a -35 region, the second consensus region comprises a -10 region and the linker sequence comprises at least 14 - 20 nucleotides and is flanked by the first consensus region and wherein the -35 region and the -10 region each include between 4 - 6 conserved nucleotides of corresponding consensus regions of the promoter (see page 17, lines 15-35, of Jensen, who expressly teaches placement of a –10 and –35 region, with conserved sequences between these regions)

f) a nucleic acid fragment homologous to the downstream region of the +1 transcription start site of the promoter (see page 21, lines 9-25 of Jensen and figure 2 of Israelsen above, which discuss the presence of the promoterless beta-galactosidase gene adjacent to the promoters).

With regard to claim 23, Israelsen includes a ribosome binding site between the –10 region and the +1 region, therefore the vector of Jensen inherently includes such a site.

With regard to claim 24, Israelsen includes a start codon between the –10 region and the +1 region, therefore the vector of Jensen inherently includes such a site.

With regard to claim 26, Jensen teaches degenerate sites at the –35 positions (see page 18, lines 1-45).

With regard to claim 27, Jensen teaches degenerate sites at the –10 positions (see page 18, lines 1-45).

Jensen in view of Israelsen do not teach the use of site specific recombination for formation of the promoter libraries.

Elledge teaches the use of site specific recombination in the place of cloning (secolumn 1, line 60 to column 2, line 16).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the use of cloning sites as taught by Jensen for creation of the promoter library with the use of recombinase sites as taught by Elledge since Elledge notes "The present invention provides compositions and methods that comprise a system for the rapid subcloning of nucleic acid sequences in vivo and in vitro without the need to use restriction enzymes (see column 13, lines 26-29)."

Elledge specifically appreciates the improvement in promoter analysis methods such as those of Jensen, noting "One might also wish to express the gene under the regulation of different promoters in a variety of organisms or to mark it with different epitope tags to facilitate subsequent biochemical or immunological analysis (see column 13, lines 52-55)." An ordinary practitioner, interested in improving the promoter libraries of Jensen to permit easier analysis of promoters, would have been directly motivated by Elledge to use the recombinase method since Elledge teaches that analysis of different promoters is within the scope of the improvement. Finally, Elledge notes "This system, together with the other methods and compositions of the present invention discussed

herein, provide a multifaceted approach for the rapid and efficient generation and manipulation of recombinant DNA, thus making possible parallel processing of whole genome sets of coding sequences (see column 14, lines 23-28)."

An ordinary practitioner, motivated to analyze promoter libraries by Jensen, would have been motivated to replace the use of restriction enzymes and cloning which pervade Jensen with the use of recombinase sites as taught by Elledge since Elledge expressly directs the practitioners attention to using this system for analyzing different promoters and since Elledge teaches that the recombinase system is rapid, efficient and permits parallel processing of large sets of sequences as in the libraries of Jensen.

8. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jensen et al (WO 98/07846) in view of Israelsen et al (App. Environ. Microbiol. (1995) 61(7):2540-2547) and further in view of Elledge et al (U.S. Patent 6,828,093) and further in view of Carrier et al (Biotechnology Progress (1999) 15:58-64).

Jensen in view of Israelsen and further in view of Elledge teach the limitations of claims 22-24, 26 and 27 as discussed above.

Jensen in view of Israelsen and further in view of Elledge do not teach the use of stabilization sequences.

Carrier teaches that stabilization sequences improve the expression of recombinant genes (see abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the stabilization sequences of Carrier in the promoter libraries of Jensen in view of Israelsen and further in view of Elledge since Carrier notes "The introduction of stabilizing elements can provide control of mRNA stability ranging over an order of magnitude and could prove to be a valuable tool in recombinant gene expression control (see page 63, column 2)." An ordinary practitioner would have been motivated to add stabilizing elements such as those of Carrier to the libraries of Jensen in view of Israelsen and further in view of Elledge in order to improve mRNA stability and increase expression, permitting better analysis of the promoters.

Conclusion

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Mauro et al (WO 01/55369) is also relevant to the claims. Mauro has separate discussions of promoters, IRES sites (the main focus of the patent) and recombinase sites in the cloning system.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jeffrey Fredman
Primary Examiner
Art Unit 1637
6/1/07